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Relating compound toxicity to molecular structure using machine learning

Master Thesis

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Abstract

Abstract goes here.

Acknowledgments

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I would like to express my sincere gratitude to my supervisor Dr. Kasia Arturi from Swiss Federal Institute of Aquatic Science and Technology (Eawag) and my supervisors Dr. Eliza Harris, Lili Gasser from SDSC for their numerous discussions, patience and valuable insights. Without their help, this thesis would not have been achievable.

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Contents

Chapter 1

Introduction

1.1 The Challenge of Environmental Pollution

Over the past few decades, the upsurge in environmental pollution by chemical compounds has been driven by industrial processes, agricultural methods, our consumerism and various other contributing factors. This has resulted in significant ecological and health issues. Although these chemicals are integral for many products and have the potential to improve our comfort of modern society, they can also pose risks and adversely affect both our health and the environment, either acutely or chronically. Toxic substances threaten wildlife but also makes our air, soil and finally our drinking water and food supply less safe. The EU currently maintains comprehensive chemical regulations, however, it is anticipated that global chemicals production will double by 2030 [1]. Moreover, the widespread utilization of chemicals, including their inclusion in consumer goods, is expected to expand further. Even though there are over 275 million known chemical compounds registered by the Chemical Abstracts Service (CAS) [2], merely a tiny fraction of them undergo close monitoring via target analytical approaches and even less is known about their toxicity profiles and negative health effects on our organsims.

Building upon the European Green Deal [3], the 8th Environment Action Programme, guiding European environmental policy until 2030, reinforces the EU's goal of sustainable living within planetary limits, with a vision extending to 2050. One of its key objectives is a zero-pollution commitment, covering air, water, and soil, prioritizing the well-being of EU citizens. In particular, the European Commission published a sustainability-focused chemicals strategy (CSS), aligning with the EU's zero-pollution ambition with one of the objectives to minimize concerning substances by either substituting or phasing them out wherever feasible [4]. Consequently, the urgent need to monitor and effectively assess the hazards associated with the daily entering of thousands of poorly understood chemicals into our

environment becomes increasingly evident.

1.2 The Imperative for Prioritization and Toxicity Assessment

Modern analytical methods, especially high-resolution mass spectrometry (HRMS/MS), are becoming increasingly important in fields like metabolomics, drug discover, forensics and environmental science and toxicology. Nontarget HRMS/MS has improved the ability to detect emerging compounds in environmental samples, often with unknown toxicity profiles. These compounds are assessed based on factors such as abundance and fragmentation data. See in Figure 1.1 for an overview. However, the endeavor to identify compounds and characterize their toxicity remains a resource-intensive and time-consuming process. This challenge is further impeded by the scarcity of well-characterized substances that can be used as references for comparison when analyzing unknown compounds, hindering comprehensive elucidation. Traditionally, the prioritization of unidentified compounds rely on signal intensity as a guiding metric. Unfortunately, this approach falls short in delivering an accurate assessment of environmental exposures, as it tends to overlook the crucial toxicological dimension. Consequently, substances with the potential for severe ecological consequences, such as endocrine-disrupting compounds, frequently evade detection due to their low abundance, despite their high toxicity. Therefore, there is an urgent need for alternative hazard-driven prioritization strategies of unidentified NTS HRMS/MS signals that incorporate the toxicity and ecological impact more effectively.

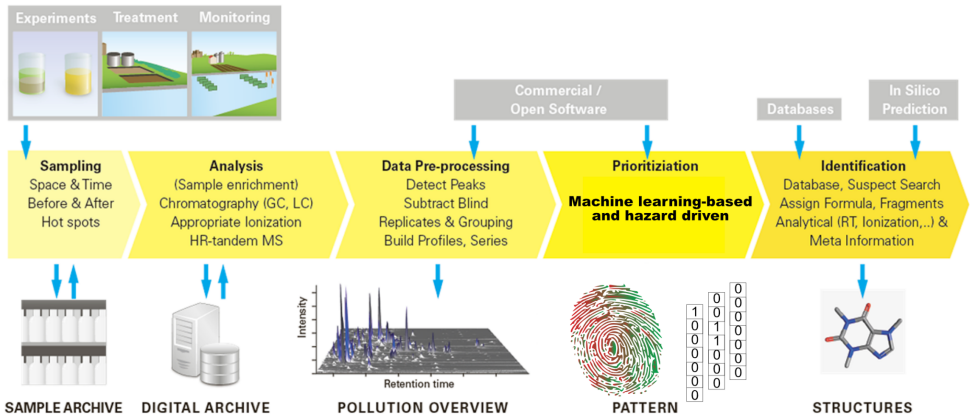


Figure 1.1: Figure 1 adapted (with modified Prioritization step) from Hollender et al. [5]: Nontarget screening with high resolution mass spectrometry in the environment: Ready to go?

1.3 The Promise of Machine Learning in Toxicity Prediction

In the past few years, machine learning has emerged as a transformative force in the field of toxicology, particularly in the realm of high-throughput toxicity prediction. High-throughput screening (HTS) has revolutionized the way we assess toxicity by allowing thousands of in vitro bioassays to be conducted rapidly. This high-throughput approach, coupled with advancements in robotics and automated analysis, has generated large volumes of toxicity data, paving the way for more comprehensive assessments of chemical compounds. Alongside the rise of machine learning, this advancement has facilitated the creation of predictive models capable of forecasting compound toxicity based on their chemical structure. These models can be trained on extensive datasets containing well-documented toxicity information, allowing them to learn the underlying patterns and relationships between chemical structure and target toxicity. Once trained, these models can reliably predict the toxicity of new compounds, even if they have not undergone laboratory testing. This approach holds the potential to significantly reduce the time and cost associated with early-stage toxicity pre-assessment and plays a crucial role in prioritizing compounds for further in-depth testing.

1.4 MLinvitroTox: A Novel Approach

In response to the pressing need for a more hazard-driven and comprehensive assessment of environmental contaminants, Arturi et al. introduced MLinvitroTox [6], an innovative machine learning framework. In particular it is the primary goal of this thesis to collaborate with the authors in further advancing and developing this framework. MLinvitroTox leverages molecular fingerprints extracted from fragmentation spectra [1], marking a fundamental shift in how we forecast the toxicity of the myriad unidentified HRMS/MS features. While traditional QSAR models predict bioactivities based on molecular fingerprints derived from chemical structures, MLinvitroTox was trained with supervised classification models on molcular fingerprints from chemical structures but is applied to molecular fingerprints generated from experimentally measured MS2 spectra using *SIRIUS* and *CSI:FingerID*. SIRIUS is a software package for annotating small molecules from nontarget HRMS/MS data, while CSI:FingerID is a machine-learning tool employed by SIRIUS to predict molecular fingerprints from fragmentation spectra. MLinvitroTox leverages streamlined machine learning techniques to predict the compounds bioactivity, respectively toxicity, ensuring a broad toxicological coverage encompassing nearly 300 target-specific and 90 cytotoxic endpoints, sourced from ToxCast/Tox21 data. Subsequently, the toxicity predictions generated

[1] also termed as Tandem mass spectrometry or MS/MS or MS2

by the framework are employed to prioritize compounds, with the flexibility to emphasize specific aspects of toxicity profiles tailored to individual preferences. This prioritization strategy facilitates more streamlined and thorough evaluations of environmental contaminants, enhancing a more hazard-driven risk assessment.

Kommentar (zentrale Frage, todo: für mich nicht ganz klar): Verständins vom Anwendugszweck von MLinvitroTox noch nicht ganz klar. Warum berechnet man nicht einmalig eine vollständige Tabelle mit allen potenziellen Chemikalien die im MS2 Spektrum auftreten könnten und predicted deren toxicity fingerprints und kann dann für neue environment samples einen simplen Lookup machen? Anstatt die toxicity profiles jedes Mal aufs Neue zu predicten mit einer pipeline und dann eine hazard-driven prioritization vornehmen? Meine Frage ist, wenn man die Rangliste von Chemikalien hat, sortiert nach Toxicity, warum kann man nicht einfach danach statisch priorisieren mit einem purem hazard-driven approach, warum braucht es dann eine dynamische pipeline?. Welche Komponente fehlt in dieser Logik damit die pipeline nötig ist? Vielleicht wenn neue Chemikalien/Daten dazu kommen. Will man das, weil der User den Fokus auf Toxicity-fingerprint anders legen will und dann basierend auf diesen Variabel, die Menge an Chemikalien für weiterführende gründliche analytische Tests anders priorisiert ist? Zum Beispiel, fokusiere auf Chemikalien, die ein hohes Risiko auf unser Hormon-System haben? Aber gleichermassen auch hier kann die Annahme gemacht werden, dass die toxicity fingerprints bekannt (predicted ahead) sind, wenn man das einmal gemacht hat für alle Chemikalien. Dann würde aus meiner Sicht ein einfaches Programm reichen für den Anweduungsfall, das nur die gewünschten Abschnitte (target) des toxicity fingerprint fokusiert und dann die Chemikalien nach target Toxicity sortiert und dies die besagte Priorisierung ist? Oder ist das zu einfach gedacht?

1.5 Objectives and Significance

The central objective of this thesis is to develop a streamlined framework for the prediction of compound toxicity across multiple endpoints, resulting in the creation of toxicity fingerprint. The generated toxicity fingerprints will provide valuable insights for the prioritization process in identifying most hazardous compounds found in environmental samples, ultimately contributing to the preservation of ecosystems and our health. The framework aims to develop a custom curation of structural and toxicological data to address challenges from modeling heterogenuous, and imbalanced data sets. Notably, the use of SIRIUS molecular fingerprints and xgboost (Extreme Gradient Boosting) models, complemented by feature selection?, has yielded consistently successful results. Furthermore, we have validated the effectiveness of MLinvitroTox by applying it to MassBank spectra, demonstrating an

average balanced accuracy of 0.75? in predicting toxicity.

1.6 Thesis Structure

The initial chapters lay the groundwork by providing essential background information and summarizing related work. As we progress through the subsequent chapters, we will delve into the methodology and technical intricacies involved in preparing ToxCast/Tox21 toxicity data, transforming them into suitable inputs for our machine learning pipeline. This foundational work will serve as the cornerstone for the forthcoming chapters, where we will showcase the potential of MLinvitroTox. Additionally, will also demonstrate the framework's effectiveness through validation using real-world data and discuss about the implications of our research.

Chapter 2

Background

We present the background information necessary to understand the rest of the thesis. We start with outlining the significance of the latively recent lab experimentation innovation of high-throughput screening (HTS), used in field of biochemistry. We introduce the ToxCast's invitro database together with tcpl to get familiar with the toxicity data used for MLinvitroTox. We then introduce the concept of molecular fingerprints and the SIRIUS molecular fingerprinting tool. We conclude with a brief introduction to machine learning and the concept of multi-task learning.

2.1 High-throughput screening and QSAR models

In the realm of high-throughput screening (HTS), a multitude of in vitro bioassays can be executed, facilitated by a combination of robotic devices, automated analysis, and data processing, resulting in the generation of extensive toxicity datasets. Following the influential publication titled "Toxicity Testing in the 21st Century: Vision and Strategy" by the U.S. National Academy of Sciences in 2007, a significant paradigm shift in toxicity testing led to the emergence of HTS toxicity databases like ToxCast and Tox21. While HTS's primary objective was to replace animal-based in vivo studies with computational and mechanistic investigations, it also paved the way for promising applications of machine learning (ML) in predictive computational toxicology. One notable avenue is the prediction of toxicity from chemical structures using Quantitative Structure–Activity Relationships (QSARs) via molecular fingerprints. Molecular fingerprints represent molecules through binary vectors of fixed length, with each bit indicating the presence (1) or absence (0) of specific substructures or functional groups. The utilization of in vitro data for toxicity prediction is based on the assumption that molecular toxic effects result from relatively straightforward interactions between distinct chemical components and receptors during a molecular initiating

event (MEI), allowing to map aslo target toxicity to the presence or absence molecular subsubstructure, encoded in the fingerprints. On the bigger biological scale the MEI can initiate a series of key events (KE) within cells which can potentially culminate in an adverse outcome pathway (AOP) at the organ or organism level, as illustrated in Figure X. Todo: Explain Mecahnistic target. The Adverse Outcome Pathway (AOP) concept provides a structured framework for organizing our understanding of the biological mechanisms that underlie toxic effects. It enables the connection of molecular initiating events to adverse outcomes, making it a valuable tool for comprehending toxicity mechanisms and innovating toxicity testing methods. Additionally, the AOP concept serves as a beneficial resource for regulatory decision-making, facilitating the identification and prioritization of chemicals for additional testing and the development of novel toxicity testing approaches. Within the Adverse Outcome Pathway (AOP) context, mechanistic targets are specific biological elements or events that are part of the sequence from a molecular initiating event (MIE) to an adverse outcome. They are pivotal components in the AOP framework, elucidating how a chemical or stressor leads to an adverse effect. Identifying mechanistic targets in an AOP is essential for comprehending the causal mechanisms underpinning adverse outcomes, offering insights into perturbed biological processes. These targets serve as potential intervention points and inform decisions related to chemical safety, risk assessment, and targeted toxicity testing approaches.

2.2 InvitroDB

The most recent release of the ToxCast's (Toxicity Forecaster) database, referred to as invitroDBv3.5, serves as a source of an extensive collection of high-throughput screening (HTS) targeted bioactivity data. This database encompasses information on a total of 9541 compounds, selectively screened across 2205 assay endpoints. This resource originated from the collaboration of two prominent institutions: the United States Environmental Protection Agency[1] (EPA) through its ToxCast program and the National Institutes of Health[2] (NIH) via the Tox21[3] initiative. Utilizing data gathered from various research laboratories, this relational database is publicly available and can be downloaded[4] by visiting the official ToxCast website.

[1] https://www.epa.gov
[2] https://ntp.niehs.nih.gov/whatwestudy/tox21
[3] https://tox21.gov/
[4] https://www.epa.gov/chemical-research/exploring-toxcast-data

2.3 Tcpl

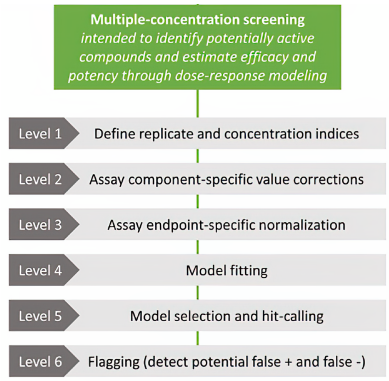
In chapter 1 we introduce the Python reimplementation *pytcpl* of the core components of the ToxCast pipeline *tcpl*, originally an R package. The tcpl package offers a comprehensive suite of tools for handling HTS data and concentration-response modeling. The multiple-concentration screening paradigm intends to pinpoint the activity of compounds, while also estimating their efficacy and potency. The concentration-response modeling procedure was specifically designed to address the characteristcally saturating response curve of molecules binding to a receptor. The modeling also aims to address outlier robustness and signal loss due to cytotoxicity.

To streamline cross-experiment comparisons and reduce parameter complexity, concentration-response modeling adheres to a zero-centered, positive response paradigm. Negative response data undergoes inverse transformation during normalization. To ensure robustness without data exclusion, a log-likelihood function utilizing a Student's t-distribution with 4 degrees of freedom [7] is employed. The model with the lowest Akaike Information Criterion (AIC) value is selected as the *winning* model. The winning model is then used to estimate the efficacy and potency of the compound. The potency estimates, also called point-of-departure (POD) estimates, are derived from the fitted curve characteristics, identifying concentrations at which the model curve crosses certain response levels. For example, the activity concentration at which the compound reaches 50% of its maximum response is denoted by *ac50* and similarly the activity concentration at cutoff efficacy by *acc*. Addionionally, the package calculates assay noise by computing the median absolute deviation over response values from the first two concentrations (bmad). The baseline region is defined as $0 + 3bmad$, and *acb* is the concentration where the model first reaches 3bmad. The figure illustrates the four POD estimates. To classify[5] a concentration-response series as an active hit and allowing to determine PODs, the following criteria must be met: The *winning* model must be either the Hill or gain-Loss model, with modeled curve's peak surpassing the assay-specific efficacy cutoff, and at least one concentration should have a median response exceeding this threshold. Notably, no POD estimates are computed when the compound is considered inactive[6], as these estimates are not applicable in such cases.

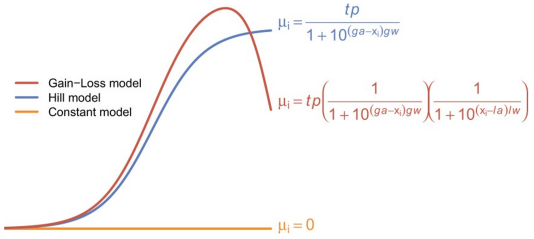
2.3.1 Tcplfit2

To improve upon tcpl, R package *tcplfit2* was developed, a standalone package focused on curve-fitting and hit-calling. The package also offers a more flexible and robust fitting procedure, allowing for the use of different opti-

[5] legacy tcpl employs only binary classification
[6] if the *winning* fit model was the constant model



(a) Overview of tcpl's data analysis pipeline for multiple concentrations screening data.



(b) Employed models in legacy tcpl for fitting concentration-response data series through the application of maximum likelihood estimation: Each data series is evaluated using three models: A constant model at zero (orange). A constrained 3-parameter Hill model (blue). A constrained 5-parameter gain-loss model (red).

Figure 2.1: tcpl

mization algorithms and the incorporation of user-defined constraints. (Todo: Explain MLE, Compare Strictly standardized mean difference.) The package also includes a more comprehensive set of POD estimates, including the *ac10* and *ac95* estimates. Tcplfit2 differs from other R-language open-source concentration-response packages like *drc* and *mixtox*, as it is specifically tailored for HTS concentration-response data, offering an extensive set of curve models, summarized in Table 2.1.

Table 2.1: All curve fitting models for tcplfit2

Model	Equation
Constant	$f(x) = 0$
Linear	$f(x) = ax$
Quadratic	$f(x) = a\left(\frac{x}{b} + \left(\frac{x}{b}\right)^2\right)$
Power	$f(x) = ax^p$
Hill	$f(x) = \frac{tp}{1+\left(\frac{ga}{x}\right)^p}$
Gain-Loss	$f(x) = \frac{tp}{\left(1+\left(\frac{ga}{x}\right)^p\right)\left(1+\left(\frac{x}{la}\right)^q\right)}$
Exponential 2	$f(x) = a\left(\exp\left(\frac{x}{b}\right) - 1\right)$
Exponential 3	$f(x) = a\left(\exp\left(\left(\frac{x}{b}\right)^p\right) - 1\right)$
Exponential 4	$f(x) = tp\left(1 - 2^{-\frac{x}{ga}}\right)$
Exponential 5	$f(x) = tp\left(1 - 2^{-\left(\frac{x}{ga}\right)^p}\right)$

2.4 Molecular Fingerprints

We

Chapter 3

Related work

A recent review highlights the proliferation of research employing invitroDB since 2006, encompassing topics such as assessing chemical toxicity, identifying contaminants for environmental monitoring, and computational toxicity forecasting. The majority of ML applications based on invitroDB have predominantly concentrated on specific target endpoints and cytotoxicity. Notably, research has extensively covered adverse outcomes related to endocrine receptor systems, including androgen and estrogen receptors, alongside areas such as carcinogenicity, hepatic steatosis, hepatotoxicity, immunotoxicity, developmental toxicity, neurotoxicity, and cardiotoxicity.

Typically, various mathematical models or curve shapes are employed to analyze the data for the best fit. Several commercial tools and open-source libraries are available for this purpose. One widely used system for managing high-throughput screening (HTS) concentration-response data is tcpl (ToxCast Pipeline), but also.

Compared to similar efforts in the field where ecotoxicity was predicted from MS2 based on in vivo data, in the current work, the invitroDB toxicity database was used to train supervised classification models for hundreds of available toxicity endpoints

In their systematic investigation using Tox21 data, Wu et al. (2021) explored the impact of various modeling approaches and chemical features on predictive toxicology, with a focus on model performance and explainability trade-offs. The study found that the assay endpoint from the Tox21 data being predicted was the most significant factor influencing model performance. Endpoints with higher predictability, characterized by lower data imbalance and larger datasets, performed well regardless of the modeling approach or molecular representation. For less predictable endpoints, simpler models like Linear Regression performed similarly to complex ones, prioritizing both predictivity and interpretability. Moreover this study suggests consensus

modeling and multi-task learning to enhance predictability and model performance across endpoints. In this thesis, we set the goal to not overlook simpler models due to their higher interpretability and comparable performance. As suggested we do not further investigate on the differnt molecular representations and use a fixed compilation of molecolar fingerprints[1] as initial input features. We incorporated in our studies a form of consensus modeling to consolidate predictability and multi-task learning to improve model performance across different endpoints.

[1] SIRIUS

Chapter 4

Material and Methods

4.1 Data Overview

Presence Matrix

Consider a collection of m assay endpoints, denoted by $A = \{a_1, a_2, \ldots, a_m\}$ and a set of n compounds represented as $C = \{c_1, c_2, \ldots, c_n\}$. To facilitate data comprehension, we introduce a *presence matrix* $P \in \{0,1\}^{m \times n}$. Rows, indexed by i, represent assay endpoints a_i, while columns, indexed by j, denote presence (1) or absence (0) of compound c_j in those endpoints. Matrix P is sparse due to the selective testing of compounds across different assay endpoints. A compound is considered present in an assay endpoint if it has undergone testing and a corresponding concentration-response series is available. See Figure 4.1 for a visual of the *presence matrix P* covering all assay endpoints and compounds in *invitroDBv3.5*.

Subsetting data

We exclusively consider assay endpoints that have been tested with a minimum of 2000 compounds. This criterion ensures the availability of sufficient data for the training of a machine learning model. Refer to Figure 4.2 for a visual representation of the *presence matrix P*, which now encompasses only the resulting subset of all assay endpoints within *invitroDBv3.5*. From now on, we will call this specific subset the data that we will be focusing on for this thesis.

Concentration-Response Series

A *concentration-response series* is represented as a set of k concentration-response pairs:

$$S = \{(conc_1, resp_1), (conc_2, resp_2), \ldots, (conc_k, resp_k)\}$$

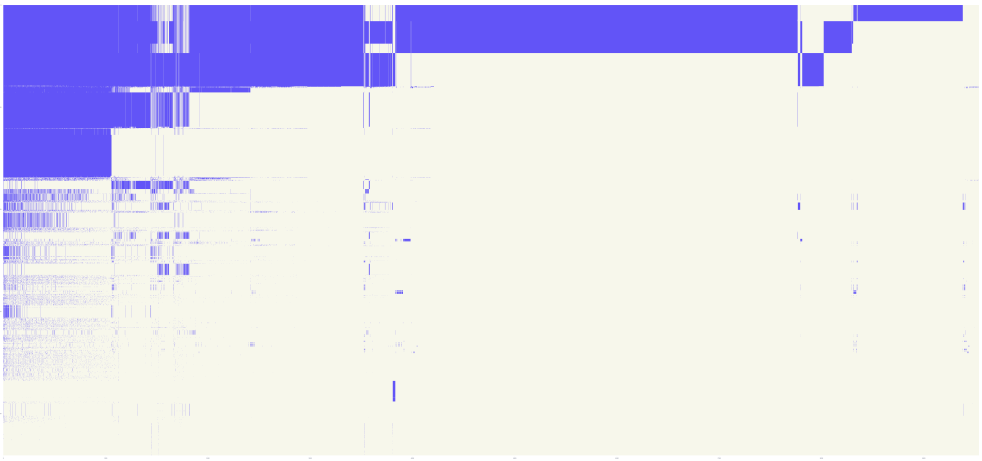


Figure 4.1: The *presence matrix* P covering all assay endpoints and compounds available in *invitroDBv3.5* with $m = 2205$ assay endpoints and $n = 9541$ compounds. The presence matrix is organized by sorting it based on the number of compounds present in each assay endpoint and the compounds are arranged in descending order of their presence frequency. The total count, where $P_{ij} = 1$, indicates the availability of 3 342 377 concentration-response series for downstream analysis.

For each entry in the presence matrix P with $P_{ij} = 1$, we collect the corresponding concentration-response series S_{ij} for the compound c_j in the assay endpoint a_i. We analyse in total $\sum_{i,j} P_{ij} = 1\,372\,225$ concentration-response series, comprising a sum of $\sum_{i,j} |S_{ij}| = 48\,861\,036$ concentration-response pairs across all compounds and assay endpoints. We get the concentration-response pairs by combining tables mc0, mc1, and mc3 from invitroDBv3.5. We also gather necessary sample information such as well type, row, and column index from the assay well-plate. The concentrations are transformed to the logarithmic scale using the unit μM (micromolar), while the responses are normalized to either fold-induction or percent-of-control units. Figure 4.3 showcases a single concentration-response series for some compound tested within an assay endpoint.

In this section, we demonstrate the significance of variations in concentration-response pairs among different compounds and assay endpoints. In practice, concentrations are often subjected to multiple testing iterations, resulting in the formation of distinct concentration groups. Within each concentration group, the number of replicates is indicated by n_{rep}. We introduce the following quantities corresponding to a concentration-response series for a compound c_i in a given assay endpoint a_i:

- $n_{\text{datapoints}_{i,j}}$: the total number of concentration-response pairs ($|S|$)
- $n_{\text{groups}_{i,j}}$: the number of distinct concentrations tested

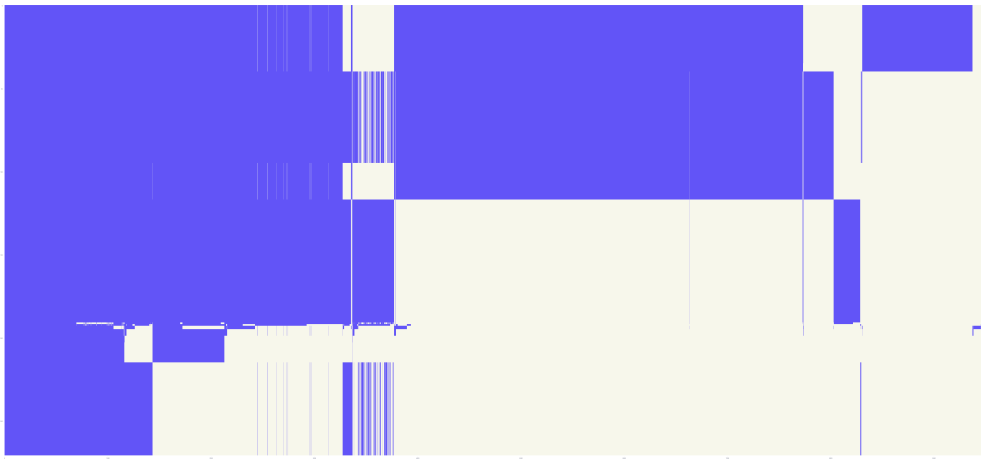


Figure 4.2: The *presence matrix* P covering only the subset of all of assay endpoints available in *invitroDBv3.5*, considered for this thesis, encompassing $m = 271$ assay endpoints and $n = 9456$ compounds. The total count, where $P_{ij} = 1$, indicates the availability of 1 372 225 concentration-response series for downstream analysis.

Figure 4.3: A concentration-response series for the compound *Estropipate* (DTXSID3023005) in the assay endpoint *TOX21_ERa_LUC_VM7_Agonist* (aeid=788). The series has a total of $k = 45$ concentration-response pairs and is composed of $n_{conc} = 15$ concentration groups, each with $n_{rep} = 3$ replicates.

- $n_{\text{replicates}_{i,j}}$: the number of replicates for each concentration group
- $min_{\text{conc}_{i,j}}$: the lowest concentration tested
- $max_{\text{conc}_{i,j}}$: the highest concentration tested

For an overview of these quantities across the entire set of considered concentration-response series, please refer to Figure 4.4. This figure illustrates the above metrics aggregated by their means, grouped by assay endpoints

and compounds.

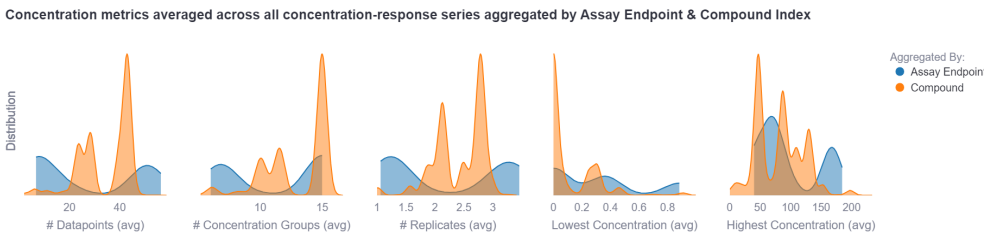


Figure 4.4: Concentration metrics averaged across all concentration-response series aggregated by assay endpoint (blue) and compound (orange). E.g., the first chart shows the distribution on the average number of datapoints across all assay enpoint $a_i \in A$ with $\frac{1}{|C|}\sum_j n_{\text{datapoints}_{i,j}}$ and across all compounds $c_j \in C$ with $\frac{1}{|A|}\sum_i n_{\text{datapoints}_{i,j}}$. The same is done for the other metrics: $n_{\text{groups}_{i,j}}$, $n_{\text{replicates}_{i,j}}$, $min_{\text{conc}_{i,j}}$, and $max_{\text{conc}_{i,j}}$.

4.2 Pytcpl

We introduce pytcpl, a streamlined Python package inspired by the R package tcpl, designed for processing high-throughput screening data. The package primarily focuses on providing essential features such as concentration-response curve fitting and allows for continuous hit-calling for compound bioactivity across diverse assay endpoints, akin to tcplfit2. Invitrodb version 3.5 release can optionally serve as backend database if desired. The package optimizes data storage and provides compressed raw data and metadata from *invitroDB* in Parquet files. This efficient strategy reduces storage needs, resulting in just 4 GB within the repository—compared to the original 80 GB database. This obviates the need for a cumbersome, large-scale database installation, rendering downstream analysis more accessible and efficient. Our package is crafted to accomodate cusomizable processing steps and facilitate interactive data visualization with curve surfer. Moreover, it empowers Python-oriented researchers to seamlessly engage in data analysis and exploration.

4.2.1 Pipeline

1. Data collection
2. Cutoff determination and filtering (Meet conditions for curve fitting)
3. Curve fitting
4. Hit calling

Data Collection

First, all datapoints are collected from the database and assigned to the concentration response-series belonging to the respective compound in the corresponding assay endpoint.

Curve Fitting

Introduce all candidate fit models, discuss the pros and cons of each model. Discuss the fitting procedure, how the models are fitted, Maximum Likelihood Estimation

Hit Calling

Akaike criterion, probability of being active, etc..

4.2.2 Curve Surfer

Data visualization, overview of what is possible with the tool. Filter by assay endpoint, compound, etc.

4.3 Machine Learning Pipeline

4.3.1 Preprocessing

Subselecting the columns from the output tables generated by pytcpl: DTXSID identifier and continuous hitcall value. The feature inputs to the machine learning model is a molecular structure represented as fingerprint generated from a SMILES string uniquely determined by the compounds DTXSID identifier. The SMILES string is a linear representation of a compound's molecular structure. The SMILES string is converted to a molecular graph, which is then converted to a feature vector. The feature vector is then used to train a machine learning model. The machine learning model is then used to predict the hitcall value for a given compound. The machine learning pipeline is illustrated in Figure **??**.

4.3.2 Binary Classification

The goal is to predict whether a compound is active or inactive for a given assay endpoint. We can formulate this as a binary classification problem, where the input is the compound's molecular structure fingerprint and the output is the hitcall value binarized by some decision threshold. The hitcall value is rendered to a binary variable, where 1 indicates that the compound is active and 0 indicates that the compound is inactive.

4.3.3 Regression

4.3.4 Massbank Validation

Chapter 5

Results and Discussion

5.1 Results

5.2 Evaluation

5.3 Discussion

Chapter 6

Conclusion

We have evidence of a multitude of chemicals being present in the environment and in our bodies and that mixture exposure indeed matters. This knowledge needs to be deepened, and the quantitative contribution of chemicals to compromised health should be better described and translated into regulatory action. As indicated in a scientific opinion paper of the German Federal Environmental Agency (Conrad et al. 2021), the CSS goals may be considered as a moving target. For increasing scientific evidence and improved method for detection and assessment of chemicals, development of new technologies require innovative regulatory, technological and societal reactions. We should be flexible and prepared to take up the scientific challenges and collaborate productively with regulatory institutions to address the identified challenges and modernise chemical risk assessment. This is also in line with the concern of many scientists that chemical pollution and the wide range of adverse effects on human and ecosystem health demand additional efforts on a global scale (Brack et al. 2022; Wang et al. 2021). We see the CSS as a European strategy that, in concert with other initiatives, may open new opportunities to minimise hazardous chemical pollution and thus risks to human health and ecosystems.

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Appendix A

Appendix

Eidgenössische Technische Hochschule Zürich
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Declaration of originality

The signed declaration of originality is a component of every semester paper, Bachelor's thesis, Master's thesis and any other degree paper undertaken during the course of studies, including the respective electronic versions.

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